Detecting early changes in choroidal vascularity and thickness using optical coherence tomography in patients with corneal crosslinking for keratoconus

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Abstract

● **AIM:** To investigate changes in choroidal thickness and vascularity in keratoconus patients treated with corneal crosslinking.

● **METHODS:** This study evaluated 28 eyes of 22 patients with keratoconus who underwent corneal crosslinking. The choroidal thicknesses were evaluated on enhanced depth imaging optical coherence tomography at the preoperative and postoperative 3d, 1, and 3mo. Choroidal thickness in the four cardinal quadrants and the fovea were evaluated. The choroidal vascularity index was also calculated.

● **RESULTS:** There was no significant difference in central choroidal thickness between the preoperative and postoperative 3d, 1mo ($P>0.05$). There was a significant increase in the 3mo ($P=0.034$) and a significant decrease in the horizontal choroidal vascularity index on the postoperative 3d ($P=0.014$), there was no statistically significant change in vertical axes and other visits in horizontal sections ($P>0.05$).

● **CONCLUSION:** This study sheds light on choroidal changes in postoperative corneal crosslinking for keratoconus. While it suggests the procedure's relative safety for submacular choroid, more extensive research is necessary to confirm these findings and their clinical significance.

● **KEYWORDS:** keratoconus; corneal crosslinking; choroidal vascularity index; enhanced depth imaging optical coherence tomography

INTRODUCTION

K eratoconus is the most common ectatic disease of the cornea, and it causes progressive central and paracentral stromal thinning, irregular astigmatism, and a decrease in visual acuity that cannot be corrected by refraction. The pathogenesis of the disease is mainly disorganization in stromal collagen fibers, formation of loose crosslinks, resulting in stromal thinning, anterior limiting membrane rupture, and central/paracentral ectasia[1]. It is seen in both sexes, is usually bilateral, and usually manifested at puberty, and it progresses until the third and fourth decade of life[2]. Corneal crosslinking (CCXL) stands out in treating keratoconus by halting the advancement of these conditions, marking a significant advance in their management[3]. The CCXL aims to create stronger crosslinks by creating oxidative deamination between corneal collagen fibrils[4].

The choroidal vascularity index (CVI) is for the quantitative evaluation of choroid vascularity, calculated upon optical coherence tomography (OCT) images[5]. It is the percentage ratio of the vascular area to the total choroidal area. The choroid is essential for the vascular supply of the retina and is frequently implicated in ocular and systemic disorders. The CVI was developed due to the need for more reliable and precise evaluations of choroidal vasculature, as previous parameters such as choroidal thickness and choroidal vessel diameter had limitations[6]. The choroid contains melanin, which absorbs ultraviolet (UV) and short-wavelength visible light and protects the retina against photodamage[7]. The retina and choroid can be damaged from too much exposure to UVA rays, especially in younger individuals (up to 30y); there might be an increased risk of retinal damage due to UVB exposure as the young human eye is more capable of transmitting UVB light compared to adults[8-9]. The average age for CCXL is about 28.4[10]. Investigating potential alterations in the retina

after CCXL is crucial since there is evidence that UV and short-wave light may be detrimental to the retina[11]. The CVI, which focuses on analyzing the vascular aspect, offers heightened sensitivity compared to computed tomography (CT) in assessing choroidal health, especially in diseases with choroidal ischemia. It surpasses CT by minimizing confounding variables, providing more reliable data, and aiding in predicting ocular diseases, thus significantly enhancing comprehension of choroidal alterations that impact retinal health, even preceding changes in conventional biomarkers[12]. However, there are few reports of CCXL's adverse effects on the choroid and retina. Regarding the intense vascularization in the choroid, vascularity measurements can give more details about its architecture and physiology since choroidal thickness alone cannot be used to evaluate the condition of choroidal vessels. In OCT scans, the CVI, which has demonstrated strong repeatability and reproducibility in prior studies, can better define the overall look of choroidal circulation[5]. There is no research on the choroidal vascularity changes in keratoconus patients treated with CCXL. This paper thoroughly analyzed early changes in subfoveal choroidal thickness and vascularity changes in patients with CCXL using spectral domain OCT (Heidelberg Spectralis, Heidelberg, Germany).

SUBJECTS AND METHODS

Ethical Approval Written consent was obtained from the participants in the study, and the Declaration of Helsinki has corresponded. The study was approved by the Bursa Uludag University ethics committee (14/02/2023-/3-44) and complied with good clinical practice guidelines.

This study is retrospective and observational. Choroidal thicknesses of 28 eyes of 22 cases diagnosed with progressive keratoconus and applied CCXL between May 2020 and July 2022 at Bursa Private Dünya Eye Hospital were evaluated on enhanced depth imaging OCT performed at the preoperative and postoperative 3d, 1, and 3mo. Those with ocular disease other than keratoconus, those with systemic disease that may affect the choroidal thickness, insufficient quality of OCT measurements, the best corrected visual acuity of less than logMAR 1.0, the spherical equivalent of more than four diopters, a spherical equivalent of more than four have keratoconus, and those who have undergone eye surgery other than CCXL, cases with hydrops and corneal scar and older patient than 35y of age were not included in the study. To weaken the accommodation during the measurements, measurements were made 10min after the patients had distant fixation and after removing their contact lenses, if any. During CCXL, the Dresden protocol was applied. The same technician took OCT measurements at visits in a regarding the preoperative measurement in both the vertical and horizontal axes. Autofocus and refractive correction features were used

in OCT measurement. Choroidal thickness was measured by an experienced ophthalmologist in a blinded fashion. Fellow eyes of patients who had received CCXL treatment to only one eye was regarded as a control group. Each subject underwent Scheimpflug tomography (Pentacam HR, Oculus, Wetzlar, Germany) and slit-lamp biomicroscopy. All topographic measurements were performed by experienced operator who were masked the clinical condition of the patient. All examinations were conducted in dark illuminated room and subjects were told to blink immediately before each measurement. Only good quality measurements were included. Diagnosis and classification of keratoconus was established by the Amsler-Krumeich classification, based on astigmatism, corneal power, corneal transparency and corneal thickness.

Surgery Protocol The same surgeon performed all CCXL cases according to the standard Dresden protocol[13]. In this protocol, patients are anesthetized with proparacaine 0.5% eye drop before the procedure. Then, central 8-10 mm of the corneal epithelium is removed (epithelium-off), and riboflavin solution (0.1% riboflavin-5-phosphate and 20% dextran T-500) is applied to the corneal surface for 30min. The cornea is then exposed to 370 nm UVA with an irradiance of 3 mW/cm for 30min. Every 5min, the riboflavin solution is reapplied. After the procedure, a therapeutic soft contact lens is placed upon the cornea, and antibiotic drops are used postoperatively. The therapeutic soft contact lens is then removed postoperative 3d. After the postoperative 3d, when the epithelization had been completed, we started topical dexamethasone drops four times per day, and the drops were discontinued after 1mo.

Spectral-Domain Optical Coherence Tomography Choroidal thickness was measured *via* the Enhanced Depth Imaging modality of the spectral domain OCT device. A seven-line scanning modality with a scan length of 9.0 mm was used in both horizontal and vertical axes. The middle scanning line of the horizontal and vertical lines' axis intersects at the deepest part of the foveola. The auto-rescan function that guides a certain reference point between different sessions was activated in all patients to reduce variations of the examined area within different sessions. All participants were asked to look at least a 6-m distance for about ten minutes to relieve possible accommodation spasms. Before the measurement for a smooth tear film, each participant blinked. During the measurement, they were instructed to focus on the same object to prevent accommodation-related alterations in choroidal thickness and ensure proper alignment of the fovea. The OCT scans were obtained before the CCXL treatment and postoperative day three following the 1 and 3mo. Each scan was carried out during a specific time window (2 *p.m.* to 6 *p.m.*) to reduce the impact of diurnal variation on choroidal thickness. Scans with poor-quality scores were repeated.
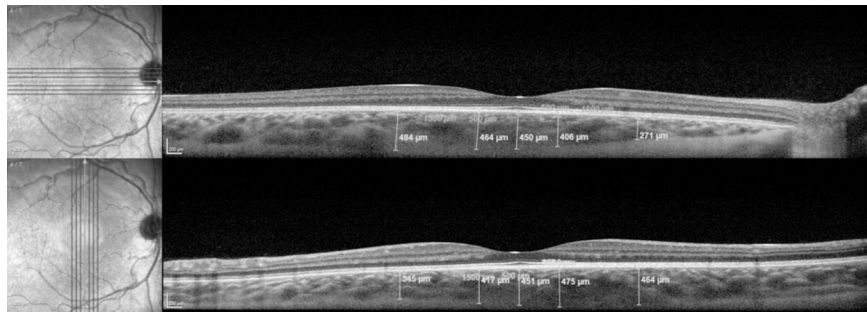
Figure 1 Choroidal thickness measurements Horizontal and vertical raster scan macula OCTs with choroidal thickness measurements are shown in upper and lower OCT scan, respectively. Measurements were taken subfoveally, and 500 µm and 1500 µm outside the fovea. OCT: Optical coherence tomography.
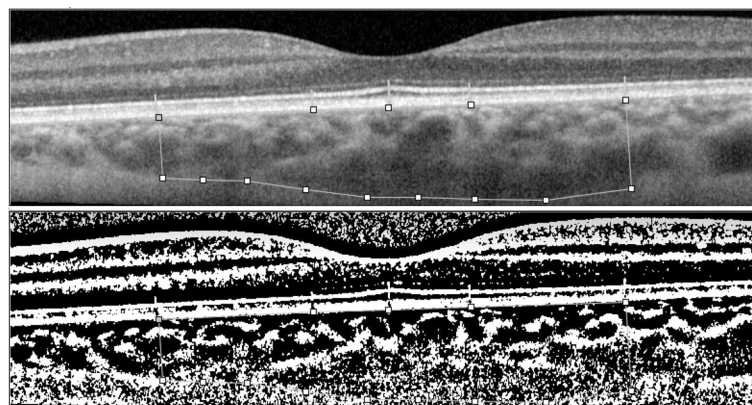
Figure 2 Choroidal vascularity index measurement In the upper OCT scan, the submacular choroid is manually marked and defined as the region of interest. The lower scan shows the processed scan used for measuring the choroidal vascularity index after applying the NiBlack autolocal threshold to the upper scan. OCT: Optical coherence tomography.

Participants underwent scans of both eyes; the unoperated fellow eyes served as controls.

Choroidal thickness was perpendicularly measured from the outermost hyperreflective retinal pigment epithelium layer to the sclerochoroidal junction manually in a 1:1 µm scale. The choroidal thickness of the 0.5 and 1.5 mm distance from the fovea in four quadrants (superior, nasal, inferior, and temporal) was measured (Figure 1). Between preoperative and postoperative sessions, the amplification effect of potential individual refractive errors was minimized using the auto-all focus feature and precise alignment for optical correction. The OCT images were exported, and for CVI measurement, the images were enrolled to Image J version v2.0.0 (National Institutes of Health, Bethesda, MD, USA; available at imagej. nih.gov/ij/). Then, CVI measurements were conducted.

Image Processing This study focused on the subchoroidal area with a width of 1.5 mm centered on the fovea, which was chosen as the region of interest (ROI). The analysis method adopted from the previous research involves selecting three choroidal vessels with a larger lumen than 100 µm randomly *via* the Oval Selection Tool on Image J. After determining the average reflectivity of these areas, converting the image to 8 bits, adjusting it with Niblack Auto Local Threshold. The binarized image was converted again to a red/green/

blue image, and the luminal area was determined using the Threshold Tool (Figure 2). The CVI was then calculated as the ratio of the luminal area to the total choroidal area. This was done to measure the eye's choroidal blood flow and vascularity[14-15]. This procedure was applied to both horizontal and vertical images. The experienced ophthalmologist who calculated the CVI is masked about patients and context of the study.

Statistical Analysis Statistical Package for the Social Sciences 28.0 software for Mac (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. $P<0.05$ were taken as statistically significant. All data were written as mean± standard deviation. The existence of a normal distribution was tested with the Shapiro-Wilk test ($P>0.05$ for the studied parameters). GᵃPower software (latest ver. 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) was used for power analysis, and the calculated sample size was 22, and the effect size was 0.78. A Wilcoxon signed-rank test compared the parameters with non-Gaussian distribution between respective visits. For Gaussian parameters, we used related samples t-test. Patients with missing data were excluded from the analysis.

RESULTS

The mean age of the cases was 23.2±4.1y (16-31y). All of the patients were from the same ethnicity (Caucasian). The

Table 1 Choroidal thickness among visits in the four quadrants with two different distances from the fovea mean±SD, μm

| Choroidal thickness	Preop.	Postop. 3d	P	Postop. 1mo	P	Postop. 3mo	P
Subfoveal	420±72	424±86	0.399[a]	428±86	0.22[a]	437±82	0.034[a]
N_{500}	395±73	400±78	0.374[a]	405±80	0.187[a]	402±85	0.296[a]
T_{500}	397±74	399±79	0.449[a]	398±94	0.48[a]	392±87	0.339[a]
I_{500}	378±82	378±73	0.479[a]	389±85	0.191[a]	382±79	0.344[a]
S_{500}	375±75	384±71	0.266[b]	399±84	0.265[b]	381±80	0.353[b]
N_{1500}	357±90	350±84	0.332[a]	356±95	0.478[a]	346±88	0.197[a]
T_{1500}	376±85	366±88	0.23[a]	362±87	0.153[a]	351±88	0.036[a]
I_{1500}	358±71	356±51	0.427[a]	367±70	0.215[a]	346±72	0.163[a]
S_{1500}	384±87	355±83[b]	0.215[a]	370±95[b]	0.084[a]	365±76	0.056[b]

Preop.: Preoperative; Postop.: Postoperative; N: Nasal; T: Temporal; I: Inferior; S: Superior. [a]Paired sample Student's *t*-test; [b]Wilcoxon signed rank test, the *P*-value is one-sided.

Table 2 Choroidal vascularity index changes in two axes every visit mean±SD, (%)

Parameters	Horizontal	P	Vertical	P
Preop. CVI	75.61±3.42		74.48±3.2	
Postop. 3rd day CVI	73.87±3.34	0.014[a]	73.78±3.22	0.436[b]
Postop. 1st month CVI	75.48±2.7	0.421[a]	74.82±2.7	0.437[b]
Postop. 3rd month CVI	76.42±3.55	0.123[b]	74.89±4.3	0.269[b]

CVI: Choroidal vascularity index; SD: Standard deviation. [a]Student's *t*-test, [b]Wilcoxon signed rank test; *P*: One-sided *P*-value; Preop.: Preoperative; Postop.: Postoperative;.

preoperative corneal evaluation revealed stage 1 keratoconus in 16 eyes, stage 2 keratoconus in 10 eyes and stage 3 keratoconus in two eyes according to Amsler-Krumreich classification. The average pachymetric measurements of the thinnest location was 459±42.5 μm and the mean of the average keratometric values were 46.3±4.01. Preoperative CTs were 420±72 μm at the center and 395±73, 397±74, 378±82, and 375±75 μm at nasal, temporal, inferior, and superior quadrants at the 500 μm away from the center, respectively. Preoperative choroidal thickness at the 1500 μm away from the center was 357±90, 376±85, 358±71, and 384±87 μm in the nasal, temporal, inferior, and superior quadrants, respectively (Table 1). Compared with the preoperative value, the choroidal thickness was decreased only in the temporal quadrant 1500 μm away from the center and decreased statistically significantly in the postoperative 3mo (*P*=0.036). There was no statistically significant difference in choroidal thickness in all quadrants during the postoperative 1wk compared to the preoperative period (*P*>0.05). In the postoperative 3mo, according to the preoperative measurements, it was observed that the central choroidal thickness increased significantly (*P*=0.034). No statistically significant difference was observed regarding choroidal thickness in all quadrants in the preoperative and postoperative periods in the fellow eyes of the treated patients who had received CCXL treatment in only one eye (*P*>0.05). The CVI changes were evaluated according to the preoperative period in the postoperative 3d, 1, and 3mo. The mean horizontal CVI were 75.61%±3.42%, 73.87%±3.34%,
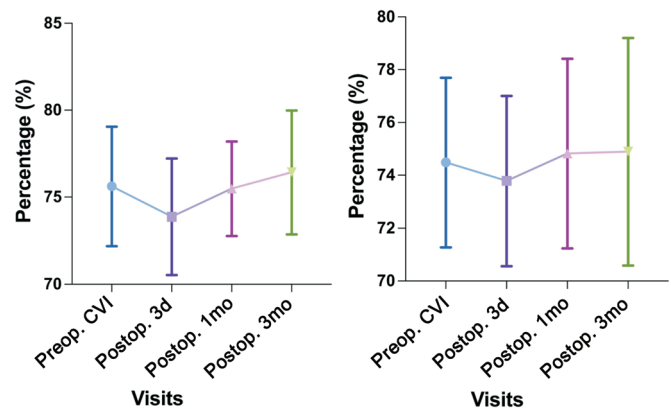
Figure 3 The changes in horizontal and vertical choroidal vascularity indices across different visits The variation of horizontal and vertical choroidal vascularity indices across different visits is illustrated (left and right, respectively). Note the decrease in the indices on the 3rd postoperative day visit, followed by a rise to values similar to preoperative levels. Preop.: Preoperative; Postop.: Postoperative; CVI: Choroidal vascularity index.

75.48%±2.7%, 76.42%±3.55% respectively. The mean vertical CVI were 74.48%±3.2%, 73.78%±3.22%, 74.82%±2.7%, 74.89%±4.3% respectively (Table 2). There were no statistically significant changes among different visits except for the postoperative 3rd-day visit in horizontal sections, according to the preoperative period (Figure 3).

DISCUSSION

In this cross-sectional study conducted to investigate the changes in choroidal thickness after CCXL, no statistically significant difference was observed between preoperative and

postoperative choroidal thicknesss, except for central choroidal thickness and temporal quadrant measurements. An increase in central choroidal thickness was observed only in the 3mo postoperatively. Nasrollahi *et al*[16] in their post-CCXL study, no statistically significant difference was observed in subfoveal choroidal thickness and choroidal volume at one month between the preoperative and postoperative periods. Still, the perifoveal quadrants were not examined separately. In the scleral crosslinking study by Sun *et al*[17] on Rhesus monkeys, the structural alterations in the macula were assessed using OCT after the monkeys had been crosslinked to the superior temporal equatorial sclera. Interestingly, in the postoperative period, at a distance of 1500 μm from the fovea temporalis, as in our study, thinning was detected in the choroidal thickness, but this thinning improved in the 1mo. However, this study commented that the thinning in the temporal quadrant was affected because it was close to the area where scleral crosslinking was performed. There was no anatomical proximity to crosslinking applied area as in the case of the Sun *et al*[17]. The cornea is more distant from the he macula when compared scleral crosslinking, yet the difference between emitted UVA radiation to macular area should be investigated between corneal and scleral crosslinking. Concerning topographic choroidal changes, accommodation decreases the thickness of the temporal choroid with an increase in axial length[18].

A prospective study by Lazaridis *et al*[19] assessed anatomical and functional alterations in the retina of the CCXL. Macular thickness has been demonstrated to decrease at the perifoveal 3 and 5 mm, and it has been hypothesized that retinal phototoxicity may be the explanation. Although only the temporal 1500 μm of our investigation showed a statistically significant decrease in choroidal thickness, it should be taken into account that this decrease can be due to the effects of UVA radiation on the retina.

The CVI can be changed in various situations like choroidal ischemia, choroiditis, age-related macular degeneration, and other retinal vascular disorders[6,20]. Choroidal ischemia may result in a decrease in CVI in subclinical age-related macular degeneration patients. CVI decrease in the postoperative 3d might be related to postoperative steroid drops. Postoperative decrease in the CVI could be related to postoperative inflammation. Corticosteroids are blamed in steroid-induced central serous chorioretinopathy patients for increased choroidal vessel permeability and subsequent increase in CVI[21]. Furthermore, Zhao *et al*[22] reported that intravitreal administration of glucocorticoids induces choroidal enlargement in rats. So, the reverse in CVI after the 3d might be related to using postoperative dexamethasone eye drops, which dampens the inflammation and enlarges the choroid. In the case of peripapillary retinal nerve fiber layer measurements, there was a reliability difference between horizontal and vertical scans[23]. Yet, the reliability of the vertical versus horizontal CVI has not been researched. So, the statistical difference between horizontal and vertical CVI's might be related to the repeatability and reliability of the measurements. In a study by Gutierrez-Bonet *et al*[24], the CVI was examined in patients with keratoconus and was significantly increased. However, no reassessment was made after treatment in these patients. Ballesteros-Sánchez *et al*[25] compared choroidal thickness measurements in patients with keratoconus who underwent CCXL. Unlike our study, choroidal thickness was measured within six months after the procedure, not on the preoperative and postoperative days. Moreover, the preoperative comparison was not made in the same patients but was directly compared with the control group. In addition, this study did not evaluate the CVI.

When we look at the limitations of our study, choroidal thicknesses were measured only in certain quadrants in the fovea and perifoveal area, so we cannot interpret these results in favor of the entire macula and posterior segment. In addition, only simple structural changes could be demonstrated with choroidal thickness and CVI, and more functional electroretinogram and angiographic features could not be presented. Also, we had some methodological limitations once we did not correlate the results of the patients with topographic parameters. In case of possible progression or regression of the keratoconus, it might affect the choroidal changes, although we corrected OCT scans with manifest refraction. The relatively small sample size is also a limitation. The data sample should be expanded to support the accuracy of the statistical inference we have obtained, and more studies are needed.

In conclusion, there are no studies on the CVI changes in patients with keratoconus who had been treated with CCXL. In our study, a statistically significant decrease in CVI was detected in the horizontal section only on the postoperative 3d of the patients, and it was observed that it did not continue at the subsequent visits. Considering that the CVI is a more reliable indicator of the choroid's dynamic state, CCXL is a relatively safe treatment method for CCXL therapy concerning submacular choroid structure and vascularity.

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